

WHAT IS CLAIMED IS:

1 1. An immunoglobulin molecule or fragment thereof comprising a region
2 where amino acid residues corresponding to at least a portion of a complementarity
3 determining region (CDR) are replaced with a peptide mimetic selected from the group
4 consisting of an EPO mimetic and a TPO mimetic.

1 2. An immunoglobulin molecule or fragment thereof according to claim 1
2 further comprising at least one flanking sequence including at least one amino acid
3 covalently linked to at least one end of the peptide mimetic.

1 3. An immunoglobulin molecule or fragment thereof according to claim 2
2 wherein the at least one flanking sequence includes a flanking sequence having a
3 proline that is covalently linked to the peptide mimetic.

1 4. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein at least two complementarity determining regions (CDRs) are replaced with
3 the peptide mimetic.

1 5. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the immunoglobulin molecule fragment is selected from the group consisting
3 of Fab fragment, F(ab')₂ fragment and ScFv fragment.

1 6. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the immunoglobulin molecule is a full IgG molecule.

1 7. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR is located on a light chain.

17. An immunoglobulin or fragment thereof according to claim 1 wherein the EPO mimetic corresponds to the sequence set forth in SEQ. ID. NO. 3.

18. An immunoglobulin molecule or fragment thereof according to claim 1 wherein the TPO mimetic corresponds to the sequence set forth in SEQ. ID. NO. 1.

19. An immunoglobulin molecule or fragment thereof according to claim 3 wherein the CDR is replaced with a peptide having a sequence including that set forth in SEQ. ID. NO. 2.

20. An immunoglobulin molecule or fragment thereof according to claim 2 wherein the CDR is replaced with a peptide having a sequence selected from the group consisting of SEQ. ID. NO. 25, SEQ. ID. NO. 27, SEQ. ID. NO. 29, SEQ. ID. NO. 31, SEQ. ID. NO. 33, SEQ. ID. NO. 35, SEQ. ID. NO. 37, SEQ. ID. NO. 39, SEQ. ID. NO. 41, SEQ. ID. NO. 43, SEQ. ID. NO. 45, SEQ. ID. NO. 47, and SEQ. ID. NO. 49.

21. An immunoglobulin molecule or fragment thereof according to claim 2 wherein the CDR is replaced with a peptide having a sequence selected from the group consisting of SEQ. ID. NO. 31, SEQ. ID. NO. 35, SEQ. ID. NO. 37, SEQ. ID. NO. 39, SEQ. ID. NO. 41, SEQ. ID. NO. 43, SEQ. ID. NO. 45, and SEQ. ID. NO. 49.

22. An immunoglobulin molecule or fragment thereof according to claim 1 wherein the immunoglobulin molecule or fragment thereof is human.

23. An immunoglobulin molecule or fragment thereof according to claim 2 wherein the immunoglobulin molecule or fragment thereof is anti-tetanus toxoid.

24. Nucleic acid encoding an immunoglobulin molecule or fragment thereof according to claim 1.

- 1 25. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 2.
- 1 26. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 21.
- 1 27. An expression vector comprising nucleic acid according to claim 24.
- 1 28. An expression vector comprising nucleic acid according to claim 25.
- 1 29. An expression vector comprising nucleic acid according to claim 26.
- 1 30. A host cell transformed with an expression vector according to claim 27.
- 1 31. A host cell transformed with an expression vector according to claim 28.
- 1 32. A host cell transformed with an expression vector according to claim 29.
- 1 33. A method of producing an immunoglobulin molecule or fragment thereof
2 comprising culturing a host cell according to claim 30 under conditions suitable for
3 expression of the immunoglobulin or fragment thereof.
- 1 34. A method of producing an immunoglobulin molecule or fragment thereof
2 comprising culturing a host cell according to claim 31 under conditions suitable for
3 expression of the immunoglobulin or fragment thereof.
- 1 35. A method of producing an immunoglobulin molecule or fragment thereof
2 comprising culturing a host cell according to claim 32 under conditions suitable for
3 expression of the immunoglobulin or fragment thereof.

- 1 36. A composition comprising an immunoglobulin or fragment thereof
2 according to claim 1 and a pharmaceutically acceptable carrier.
- 1 37. A method of engineering an immunoglobulin molecule or fragment
2 thereof to exhibit an activity of a biologically active peptide comprising:
3 providing nucleic acid encoding an immunoglobulin molecule or a
4 fragment thereof;
5 replacing at least a portion of at least one CDR encoding region with
6 nucleic acid encoding a biologically active peptide selected from the group consisting
7 of TPO mimetic and EPO mimetic to form a biologically active peptide substituted
8 nucleic acid construct; and
9 expressing the peptide encoded by the nucleic acid construct along with
10 an antibody chain selected from the group consisting of heavy chain and light chain, in
11 a suitable host cell such that a heterodimer is formed.
- 1 38. A method according to claim 37 wherein the biologically active peptide
2 includes a proline covalently attached to its carboxy terminus.
- 1 39. A method according to claim 38 wherein the biologically active peptide is
2 selected from the group consisting of SEQ. ID. NO: 31, SEQ. ID. NO: 35, SEQ. ID.
3 NO: 37, SEQ. ID. NO: 39, SEQ. ID. NO: 41, SEQ. ID. NO: 43, SEQ. ID. NO: 45, and
4 SEQ. ID. NO: 49.
- 1 40. A method of stimulating proliferation, differentiation, or growth of
2 promegakaryocytes or megakaryocytes, comprising contacting promegakaryocytes or
3 megakaryocytes with an effective amount of an immunoglobulin molecule or fragment
4 thereof having one or more CDR regions replaced with a TPO mimetic peptide.
- 1 41. A method according to claim 40 wherein platelet production is increased.

- 1 50. An immunoglobulin molecule or fragment thereof according to claim 49
2 further comprising at least one flanking sequence including at least one amino acid
3 covalently linked to at least one end of the peptide mimetic.
- 1 51. An immunoglobulin molecule or fragment thereof according to claim 50
2 wherein the at least one flanking sequence includes a flanking sequence having a
3 proline that is covalently linked to the carboxy terminus of the peptide mimetic.
- 1 52. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein at least two CDRs are fused to respective peptide mimetics.
- 1 53. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the immunoglobulin molecule fragment is selected from the group consisting
3 of Fab fragment, F(ab')₂ fragment and ScFv fragment.
- 1 54. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the immunoglobulin molecule is a full IgG molecule.
- 1 55. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is located on a light chain.
- 1 56. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is located on a heavy chain.
- 1 57. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is selected from the group consisting of CDR2 of a heavy chain and
3 CDR2 of a light chain.
- 1 58. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is selected from the group consisting of CDR1 of a heavy chain and
3 CDR1 of a light chain.

- 1 59. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein amino acid residues corresponding to a portion of more than one CDR are
3 replaced.
- 1 60. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is selected from the group consisting of a CDR3 of a heavy chain
3 and a CDR3 of a light chain.
- 1 61. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR3 regions of a heavy chain and a light chain are fused with the
3 peptide mimetic.
- 1 62. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR includes both CDR2 and CDR3.
- 1 63. An immunoglobulin molecule or fragment thereof according to claim 62
2 wherein the CDR is located in a heavy chain.
- 1 64. An immunoglobulin molecule or fragment thereof according to claim 62
2 wherein the CDR is located in a light chain.
- 1 65. Nucleic acid encoding an immunoglobulin or fragment thereof according
2 to claim 49.
- 1 66. Nucleic acid encoding an immunoglobulin or fragment thereof according
2 to claim 50.
- 1 67. An expression vector comprising nucleic acid according to claim 65.
- 1 68. An expression vector comprising nucleic acid according to claim 66.

- 1 69. A host cell transformed with an expression vector according to claim 67.
- 1 70. A host cell transformed with an expression vector according to claim 68.
- 1 71. A method of producing an immunoglobulin molecule or a fragment
2 thereof comprising culturing a host cell according to claim 69 under conditions suitable
3 for expression of the immunoglobulin or fragment thereof.
- 1 72. A method of producing an immunoglobulin molecule or a fragment
2 thereof comprising culturing a host cell according to claim 70 under conditions suitable
3 for expression of the immunoglobulin or fragment thereof.
- 1 73. A composition comprising an immunoglobulin or fragment thereof
2 according to claim 49 and a pharmaceutically acceptable carrier.
- 1 74. A method of engineering an immunoglobulin molecule or fragment
2 thereof to exhibit an activity of a biologically active peptide comprising:
3 providing nucleic acid encoding an immunoglobulin molecule or a
4 fragment thereof;
5 fusing at least a portion of at least one CDR encoding region with a
6 biologically active peptide selected from the group consisting of TPO mimetic and EPO
7 mimetic to form a biologically active peptide substituted nucleic acid construct; and
8 expressing the peptide encoded by the nucleic acid construct along with
9 an antibody chain selected from the group consisting of heavy chain and light chain, in
10 a suitable host cell such that a heterodimer is formed.
- 1 75. A method according to claim 74 wherein the biologically active peptide
2 includes a proline covalently attached to its carboxy terminus.
- 1 76. A method of stimulating proliferation, differentiation or growth of
2 promegakaryocytes or megakaryocytes comprising contacting

3 promegakaryocytes or megakaryocytes with an effective amount of an
4 immunoglobulin molecule or fragment thereof having one or more CDRs fused to
5 a TPO mimetic peptide.

1 77. A method of increasing the production of red blood cells comprising
2 contacting hemopoietic stem cells or progenitors thereof with an effective amount of an
3 immunoglobulin molecule or fragment thereof having one or more CDR regions are
4 fused to an EPO mimetic peptide.

1 78. An immunoglobulin molecule or fragment thereof comprising a region
2 where amino acid residues corresponding to at least a portion of a CDR are fused with
3 a biologically active peptide flanked with a proline at the carboxy terminus of the
4 biologically active peptide.

1 79. An immunoglobulin molecule or fragment thereof according to claim 78
2 wherein at least two CDR regions are replaced with the biologically active peptide.

1 80. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 78.

1 81. An expression vector comprising a nucleic acid according to claim 80.

1 82. A host cell transformed with an expression vector according to claim 81.

1 83. A library containing varied immunoglobulin molecules or fragments
2 thereof wherein amino acid residues corresponding to at least a portion of at least one
3 CDR are replaced with a peptide mimetic selected from the group consisting of an
4 EPO mimetic and a TPO mimetic, the peptide mimetic having at least one flanking
5 sequence which has been randomized to generate immunoglobulin molecules or
6 fragments thereof having variable amino acid sequences.

1 84. A library containing varied immunoglobulin molecules or fragments
2 thereof wherein amino acid residues corresponding to at least a portion of at least one
3 CDR are fused with a peptide mimetic selected from the group consisting of an EPO
4 mimetic and a TPO mimetic, the peptide mimetic having at least one flanking
5 sequence which has been randomized to generate immunoglobulin molecules or
6 fragments thereof having variable amino acid sequences.

1 85. An immunoglobulin molecule or fragment thereof according to claim 44
2 wherein the biologically active peptide is flanked at both its carboxy terminus and its
3 amino terminus.

1 86. An immunoglobulin molecule or fragment thereof according to claim 85
2 wherein the biologically active peptide is flanked at its carboxy terminus with an amino
3 acid sequence selected from the group consisting of proline-valine, proline-aspartic
4 acid, proline-isoleucine, serine-asparagine, serine-lysine, serine-glycine, serine-
5 arginine, leucine-histidine, leucine-glutamic acid, leucine-alanine, leucine-
6 phenylalanine, valine-glutamine, valine-serine, valine-alanine, valine-asparagine,
7 isoleucine-serine, isoleucine-tyrosine, asparagine-proline, asparagine-serine, asparagine-
8 tryptophan, asparagine-valine, phenylalanine-valine, threonine-serine, methionine-
9 alanine, arginine-serine, arginine-glycine, arginine-threonine, arginine-leucine,
10 arginine-valine, tryptophan-arginine, tryptophan-tryptophan, alanine-arginine, aspartic
11 acid-valine, glycine-tyrosine, glutamine-arginine, and glycine-lysine.

1 87. An immunoglobulin molecule or fragment thereof according to claim 44
2 wherein the biologically active peptide is flanked at its carboxy terminus with an amino
3 acid sequence selected from the group consisting of proline-valine, proline-aspartic
4 acid, proline-isoleucine, serine-asparagine, serine-lysine, serine-glycine, serine-
5 arginine, leucine-histidine, leucine-glutamic acid, leucine-alanine, leucine-
6 phenylalanine, valine-glutamine, valine-serine, valine-alanine, valine-asparagine,
7 isoleucine-serine, isoleucine-tyrosine, asparagine-proline, asparagine-serine, asparagine-
8 tryptophan, asparagine-valine, phenylalanine-valine, threonine-serine, methionine-

alanine, arginine-serine, arginine-glycine, arginine-threonine, arginine-leucine, arginine-valine, tryptophan-arginine, tryptophan-tryptophan, alanine-arginine, aspartic acid-valine, glycine-tyrosine, glutamine-arginine, and glycine-lysine.

88. An immunoglobulin molecule or fragment thereof according to claim 44 wherein the biologically active peptide is flanked at its amino terminus with an amino acid sequence selected from the group consisting of tryptophan-leucine, valine-valine, glycine-proline, leucine-proline, leucine-tyrosine, serine-leucine, serine-isoleucine, serine-proline, threonine-methionine, threonine-tyrosine, threonine-proline, glutamine-threonine, glutamine-glutamic acid, glutamine-leucine, arginine-methionine, arginine-asparagine, arginine-threonine, arginine-glycine, arginine-serine, lysine-glutamic acid, lysine-glycine, alanine-histidine, histidine-glycine, histidine-leucine and asparagine—proline.

89. An immunoglobulin molecule or fragment thereof according to claim 85 wherein the biologically active peptide is flanked at its amino terminus with an amino acid sequence selected from the group consisting of tryptophan-leucine, valine-valine, glycine-proline, leucine-proline, leucine-tyrosine, serine-leucine, serine-isoleucine, serine-proline, threonine-methionine, threonine-tyrosine, threonine-proline, glutamine-threonine, glutamine-glutamic acid, glutamine-leucine, arginine-methionine, arginine-asparagine, arginine-threonine, arginine-glycine, arginine-serine, lysine-glutamic acid, lysine-glycine, alanine-histidine, histidine-glycine, histidine-leucine and asparagine—proline.

90. An immunoglobulin molecule or fragment thereof according to claim 4 wherein the at least two CDRs are selected from the group consisting of heavy chain CDR3-heavy chain CDR2, heavy chain CDR3-light chain CDR2, heavy chain CDR2-light chain CDR2, heavy chain CDR3-heavy chain CDR2-light chain CDR2 and heavy chain CDR3-light chain CDR1.

- 1 91. An immunoglobulin molecule or fragment thereof according to claim 4
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.
- 1 92. An immunoglobulin molecule or fragment thereof according to claim 45
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.
- 1 93. An immunoglobulin molecule or fragment thereof according to claim 52
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.
- 1 94. A method of determining whether a substance has cMpl receptor activity
2 comprising:
3 co-transfecting full length cMpl receptor with a c-Fos promoter luciferase
4 reporter construct;
5 starving the cells;
6 stimulating the cells with the substance;
7 harvesting the cells; and
8 measuring luciferase activity.
- 1 95. A plasmid comprising SEQ ID NO. 111.